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A novel mutation as a cause of L-2-hydroxyglutaric aciduria

Received: 20 January 2008
Received in revised form: 16 May 2008
Accepted: 29 May 2008
Published online: 27 April 2009

Sirs: L-2-hydroxyglutaric aciduria is a rare inborn error of metabolism, in which L-2-hydroxyglutarate accumulates secondary to a deficiency in FAD-linked L-2-hydroxyglutarate dehydrogenase, a mitochondrial enzyme which usually converts L-2-hydroxyglutarate to α -ketoglutarate. The accumulation of this toxic metabolite is responsible for the clinical syndrome. The diagnosis can present in adulthood with a progressive decline in neurological function. We describe a patient who came to clinical attention following a minor head injury. Molecular analysis revealed a novel mutation leading to a premature stop codon.

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Case presentation

The patient was a 16-year-old male who carried a diagnosis from birth of "cerebral palsy". He had delayed developmental milestones in infancy, but stabilised in early childhood. His intellectual ability deteriorated at age 12, and at age 16 he developed mild tremor, ataxia of gait and seizures. Over the subsequent 8 years, he developed progressive deterioration in gait, ataxia, dysarthria and increasing seizures. At age 24 years, he suffered a minor head injury and developed a prolonged episode of loss of consciousness, followed by encephalopathy. Examination on admission revealed an enlarged head circumference (59.6 cm), bilateral ptosis, drooling, ataxic gait, and past-pointing in both upper limbs. He had a mild spastic quadraparesis. He recovered over a number of weeks to his baseline.

Investigations

EEG showed bilateral theta delta slowing. MRI showed atrophy with hypomyelination (Fig. 1). Motor and sensory nerve conduction studies were normal. Lumbar puncture revealed elevated CSF protein at 113 mg/dL (upper limit of normal 45). A metabolic screen revealed elevated levels of L-2-OH glutaric acid in urine, with the L-enantiomer measured at 1354 mmol/mol creat (normal 1.3–18.9). Genetic analysis revealed a novel mutation in the *L2 hydroxyglutarate dehydrogenase gene* (*L2HGDH*), with a C>G transversion in exon 7 (c.788C>G), which leads to a substitution of serine by a stop codon at position 263 (p. Ser263X), and a predicted loss of function of the enzyme.

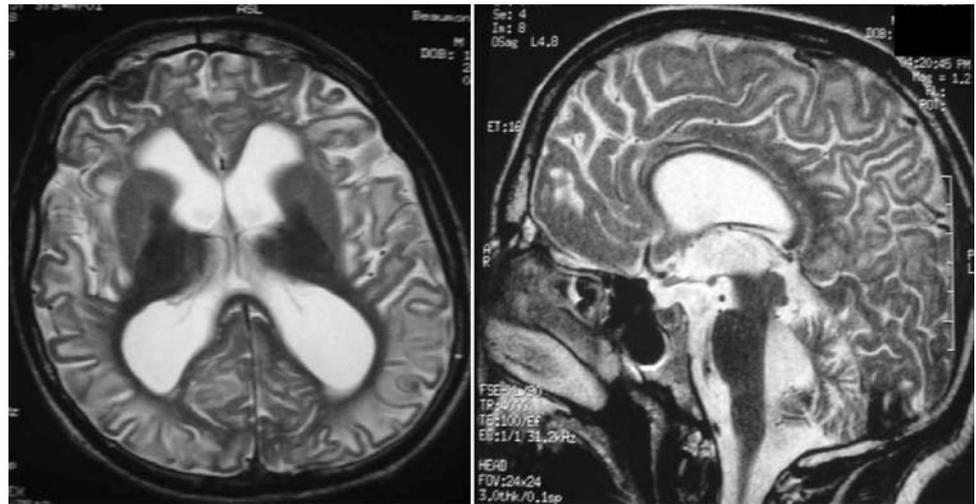
Discussion

L-2-OH glutaric aciduria was first described in 1980 [1], and over 100 cases have now been described in the literature. The age of diagnosis can vary from nine months to middle-age [2]. Diagnosis is supported by elevated levels of L-2-hydroxyglutaric acid in the urine, CSF or plasma of affected patients [3]. MRI shows sub-cortical leukoencephalopathy, atrophy of the cerebellar vermis, and involvement of the dentate nuclei [4]. MRI appearances show a good correlation with the severity of the disease. The pathological hallmarks are spongiosis and cystic cavitations in the subcortical regions [5].

L-2-OH glutaric aciduria is associated with loss of function mutations in the *L2HGDH* gene located on chromosome 14q22.17, coding for the enzyme L-2-hydroxyglutarate dehydrogenase [6, 7]. Sequencing revealed a novel homozygous mutation in *L2HGDH* gene (C>G transversion in exon 7; c.788C>G) which has not been previously described. The presence of a stop codon would predict protein truncation and complete loss of function. However, the phenotype of this patient's condition did not differ substantially from that described with other mutations.

Conclusion

L-2-hydroxyglutaric aciduria should be considered in the differential diagnosis of patients presenting with developmental delay and declining cognitive function. Patients may have an increased sensitivity to minor head trauma, although this has not been reported in the literature in other cases. As part of the diagnostic assessment, patients should have MRI scanning and analysis urine

Fig. 1 MRI of patient at 24 years

organic acids. Although broadening our understanding of the disease, novel genetic variations may not alter the clinical course.

■ **Conflict of interest** The authors declare no conflict of interest.

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